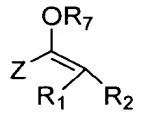


VIII

wherein Z is H, OH, YNOX, OR_5, $-NR_5R_6$ and R_1 and R_2, are as defined in claim 1; and R_7 is cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds; or $-SiR_8R_9R_{10}$;

R_8, R_9, and R_{10} are each, independently, aryl; 4-8 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S; cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds; or two of R_8, R_9, and R_{10} taken together with the silicon atom to which they are attached form a heterocyclic ring of 5 or 6 members;

in the presence of a Lewis acid or fluoride reagent in an ether organic solvent at temperatures ranging from about -78°C to about 30°C to produce an alpha-sulfonyl carbonyl compound of formula V; any reactive substituent group(s) being protected during the reaction and removed thereafter ; and further if desired isolating any chiral or stereoisomeric product as an individual isomer.

REMARKS

The present invention relates to certain alpha-sulfonyl hydroxamic acid derivatives, pharmaceutical composition containing them and a method of preparation.

Claims 1-52 have been rejected under 35 USC 102(a) as being anticipated by WO 00/71514 ("Barta"). The Examiner contends that Barta teaches the claimed sulfonyl hydroxamic acid derivatives.

Applicants respectfully traverse the rejection. Barta is concerned with beta-sulfonyl hydroxamic acid derviatives whereas the present invention relates to alpha-sulfonyl hydroxamic acid derivatives. Applicants have reviewed the passages cited by the Examiner, but do not believe that Barta anticipates the present invention.

Claims 1-44 have been rejected under 35 USC 102(b) as being anticipated by J. Org. Chem. Vol. 55, pp. 1125-1126 ("Kende").

Applicants again respectfully traverse the rejection. Although Kende is concerned with alpha-sulfonyl hydroxamic acid derivatives. Kende uses only alkyl and cycloalkyl esters. Applicants have amended the claims such that R_1 and R_2 are aryl, heteroaryl or cycloheteroalkyl. Applicants believe that the claims as amended are patentable over Kende.

Claims 1-52 have been rejected under 35 USC 112, first paragraph, because the Examiner contends that the specification while being enabling for R_1, R_2 piperdine derivative does not provide enablement for heterocyclic containing derivatives, particularly thiomorpholine derivatives.

Applicants respectfully traverse the rejection. While the Examiner is correct that Schemes I, II, and II all show the preferred piperidine group, the specification clearly indicates that these are preferred routes (see paragraph bridging pages 23 and 24). Applicants believe that one of ordinary skill in the art after reading the specification (including the schemes and examples) would be able to substitute any claimed group for the clearly depicted piperidine group without undue experimentation. Specifically in response to the Examiner's stated concern with thiomorpholides, one of ordinary skill in the art would be able to make the compounds using the process as claimed.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with Markings to Show Changes Made."**

Applicants believe that the present application is in condition for allowance and respectfully request that the Examiner enter the amendment, reconsider the rejections in light of the remarks herein and allow the application. Favorable treatment of the application is earnestly solicited.

John W. Hogan, Jr.

Reg. No. 32,703

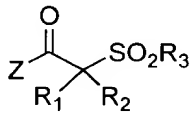
Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940
Tel. No. (973) 683-2152

Version with Markings to Show Changes Made

In the Claims

Claim 1 has been amended as follows:

1. (Amended) A method of preparing alpha-sulfonyl derivatives of the formula V:



V

wherein Z is H, OH, -NYOX, $-OR_5$ or $-NR_5R_6$;

X is hydrogen, alkyl of 1-6 carbon atoms, benzyl, hydroxyethyl, t-butyldimethylsilyl, trimethylsilyl or tetrahydropyranyl;

Y is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6 to 10 carbon atoms, 5-10 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl; wherein said alkyl, aryl, heteroaryl, cycloalkyl and cycloheteroalkyl group of Y is optionally substituted on any atom capable of substitution, with 1 to 3 substituents selected from the group consisting of halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_5R_6$,$-S(O)_nR_5$,
$-OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$,
$-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$,
$SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$,
$-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, $-SO_2NHCN$,
$-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R_1 and R_2 are each, independently, ~~hydrogen;~~ aryl of 6 to 10 carbon atoms; 5-10 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S; ~~cycloalkyl of 3-6 carbon atoms;~~ 5-10 membered cycloheteroalkyl; ~~alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon~~

~~atoms having 1 to 3 double bonds; alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds;~~ or R_1 and R_2 taken together with the carbon atom to which they are attached form ~~a cycloalkyl ring of 3-8 carbon atoms or~~ a 5-10 membered cycloheteroalkyl ring; and wherein the aryl, heteroaryl, ~~cycloalkyl,~~ or cycloheteroalkyl, ~~alkyl, alkenyl, and alkynyl.~~ may be optionally substituted on any atom capable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_5R_6$, $-S(O)_nR_5$, $-OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R_3 is alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms having 1 to 3 double bonds, alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl, aryl of 6 to 10 carbon atoms, 5-6 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O, and S; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl of R_3 may optionally be substituted on any atom capable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_5R_6$,$-S(O)_nR_5$, $-OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R_4 is hydrogen; aryl; aralkyl, heteroaryl; heteroaralkyl, alkyl of 1-6 carbon atoms; cycloalkyl of 3-6 carbon atoms; $-C(O)_nR_5$, $-CONR_5R_6$ or SO_2R_5;

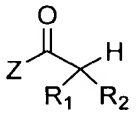
R_5 and R_6 are each independently hydrogen, optionally substituted aryl; 4-8 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S; cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms or alkynyl of 2-18 carbon atoms; or R_5 and R_6 taken together with the nitrogen atom to which they are attached may form a 5-10 membered cycloheteroalkyl ring; and

n is 1 or 2; or a pharmaceutical salt thereof,
which comprises reacting a sulfonyl fluoride of the formula III

$$R_3'SO_2F$$

III

wherein R_3' is as hereinabove defined for R_3 with the proviso that R_3' does not contain a group that can form an anion under basic conditions; with a carbonyl compound of the formula IV:

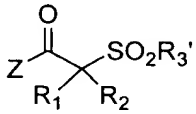


IV

wherein Z is H, OH, YNOX, $-NR_5R_6$ or OR_5, and X, Y, R_1, R_2, R_5, and R_6 are as hereinabove defined; in the presence of a metal hydride or amide base in an ether organic solvent at temperatures from about -78°C to about 30°C to produce an alpha-sulfonyl carbonyl compound of formula V;
any reactive substituent group(s) being protected during the reaction and removed thereafter; and further if desired isolating any chiral or stereoisomeric product as an individual isomer.

Claim 15 has been amended as follows:

15. (Amended) A method of preparing alpha-sulfonyl derivatives of the formula V:



V

wherein wherein Z is H, OH, -NYOX, -OR_5 or -NR_5R_6;

R_1 and R_2 are each, independently, ~~hydrogen;~~ aryl of 6 to 10 carbon atoms; 5-10 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S; ~~cycloalkyl of 3-6 carbon atoms;~~ 5-10 membered cycloheteroalkyl; ~~alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms having 1 to 3 double bonds; alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds;~~ or R_1 and R_2 taken together with the carbon atom to which they are attached form ~~a cycloalkyl ring of 3-8 carbon atoms or~~ a 5-10 membered cycloheteroalkyl ring; and wherein the aryl, heteroaryl, ~~cycloalkyl,~~ or cycloheteroalkyl, ~~alkyl, alkenyl, and alkynyl,~~ may be optionally substituted on any atom capable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, -OR_5, =O, -CN, -COR_5 , perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, -$CONR_5R_6$, -$S(O)_nR_5$, -$OPO(OR_5)OR_6$, -$PO(OR_5)R_6$, -$OC(O)OR_5$, -$OR_5NR_5R_6$, -$OC(O)NR_5R_6$, -$C(O)NR_5OR_6$, -$COOR_5$, -SO_3H, -NR_5R_6, -$N[(CH_2)_2]_2NR_5$, -NR_5COR_6, -NR_5COOR_6, $SO_2NR_5R_6$, -NO_2, -$N(R_5)SO_2R_6$, -$NR_5CONR_5R_6$, -$NR_5C(=NR_6)NR_5R_6$, -$NR_5C(=NR_6)N(SO_2R_5)R_6$, -$NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, -$SO_2NHCN$, -$SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R_3' is alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms having 1 to 3 double bonds, alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl, aryl of 6 to 10 carbon atoms, 5-6 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O, and S; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl of R_3 may optionally be substituted on any atom capable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, -OR_5, =O, -CN, -COR_5, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, -$CONR_5R_6$,-$S(O)_nR_5$, -$OPO(OR_5)OR_6$, -$PO(OR_5)R_6$, -$OC(O)OR_5$, -$OR_5NR_5R_6$, -$OC(O)NR_5R_6$, -$C(O)NR_5OR_6$, -$COOR_5$, -SO_3H, -NR_5R_6, -$N[(CH_2)_2]_2NR_5$, -NR_5COR_6, -NR_5COOR_6, $SO_2NR_5R_6$, -NO_2, -$N(R_5)SO_2R_6$, -$NR_5CONR_5R_6$,

$-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl; provided that R_3' does not contain a group that can form an anion under basic conditions;

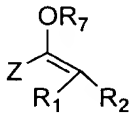
or a pharmaceutically acceptable salt thereof, which comprises the steps of :

a) reacting a sulfonyl fluoride of formula III:

$R_3'SO_2F$

III

wherein R_3' is as defined in claim 1; with an enol ether of formula VIII:



VIII

wherein Z is H, OH, YNOX, OR_5, $-NR_5R_6$ and R_1 and R_2, are as defined in claim 1; and R_7 is cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds; or $-SiR_8R_9R_{10}$;

R_8, R_9, and R_{10} are each, independently, aryl; 4-8 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S; cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds; or two of R_8, R_9, and R_{10} taken together with the silicon atom to which they are attached form a heterocyclic ring of 5 or 6 members;

in the presence of a Lewis acid or fluoride reagent in an ether organic solvent at temperatures ranging from about -78°C to about 30°C to produce an alpha-sulfonyl carbonyl compound of formula V; any reactive substituent group(s) being protected during the reaction and removed thereafter; and further if desired isolating any chiral or stereoisomeric product as an individual isomer.